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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/541,795	03/31/2000	James Link	6446.US.P2	3564

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EXAMINER

PATEL, SUDHAKER B

ART UNIT	PAPER NUMBER
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1624

DATE MAILED: 09/23/2002

12

Please find below and/or attached an Office communication concerning this application or proceeding.

# Office Action Summary

Application No.

09/541,795

Applicant(s)

James Link et al

Examiner

Sudhaker Patel

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

## Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

## Status

- 1) ☒ Responsive to communication(s) filed on Jul 29, 2002
- 2a) ☒ This action is FINAL. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 35 C.D. 11; 453 O.G. 213.

## Disposition of Claims

- 4) ☒ Claim(s) 1-60 is/are pending in the application.
- 4a) Of the above, claim(s) 2, 24, and 25 is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 1, 3-23, and 26-60 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claims \_\_\_\_\_ are subject to restriction and/or election requirements.

## Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on \_\_\_\_\_ is: a) ☐ approved b) ☐ disapproved by the Examiner.  
If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

## Priority under 35 U.S.C. §§ 119 and 120

- 13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).  
a) ☐ All b) ☐ Some\* c) ☐ None of:  
1. ☐ Certified copies of the priority documents have been received.  
2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.  
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).  
\*See the attached detailed Office action for a list of the certified copies not received.
- 14) ☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).  
a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

## Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892) 4) ☐ Interview Summary (PTO-413) Paper No(s). \_\_\_\_\_
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948) 5) ☐ Notice of Informal Patent Application (PTO-152)
- 3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s). 11 6) ☐ Other:

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### **DETAILED ACTION**

Applicants' communication paper # 10 dated 7/29/02 is acknowledged.

The claims in this application are the claims 1-60.

Applicants' remarks and arguments for traversal of restriction/election are not persuasive for prosecution of this application in the way applicants' have proposed for the reasons already stated in earlier Office Action paper # 8, dated 2/27/02.

However, after further review and reconsideration, following is examiner's position for the election/restriction.

#### **I. Election/Restriction**

- I. Claims(in part) 1,3-23,26-60, drawn to compounds, compositions, a method of use, and the first recited process of making Formula I wherein the phenyl ring is 4-substituted cinnamide, i.e. R3 = cinnamide; Ar and R3 (values consist) both = aryl i.e. nonheterocycle, classified in classes 558-568, subclasses various depending in the nature of variables on to Ar group, and R1, R2, R4, R5. Typical examples of the compounds, e.g. are compounds of Examples 382,382,386,387,401,406,410
- II. Claims(in part) 1,3-23,26-60, drawn to compounds, compositions, a method of use, and the first recited process of making Formula I phenyl ring is 4-substituted cinnamide, i.e. R3 = cinnamide; wherein one of Ar and R3 (values consist) is a 6-

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membered heterocycle with 1 N, and additionally 1-3 heteroatoms selected from N,O,S, classified in class 544, subclasses various depending in the nature of variables on to Ar group, and R1, R2, R4, R5. Majority of the compounds fall in this group, for e.g. compounds of Examples 356, 357, 358, 364,369, 381,384, 395, 397, 398, 400, 403, 405, 409, 410,411,413,414,415,416,419,421,422,423,424,425,426,427,430,431,432,435,439,441,442.

- III. Claims(in part)1,3-23,26-60, drawn to compounds, compositions,a method of use, and the first recited process of making Formula I wherein one of Ar and R3 (values consist) = is a 6-membered heterocycle with 1N i.e. piperidine, classified in class 546, subclasses various. Examples of compounds falling inthis group are, for e.g. Examples Nos. 340, 360,365,367,370,373,376,380,385,386,388,389,391,392,396,401,407,408,412,417,418,420,428,429,433,434,436,437,438,440.
- IV. Claims(in part)1,3-23,26-60, drawn to compounds, compositions,a method of use, and the first recited process of making Formula I wherein the formula I has rings like Homopiperazine, classified in class 540, subclass Rtypical examples of compounds, e.g. Examples Nos. 368,378,379.
- V. Claims(in part)1-23,26-60, drawn Formula I compounds not included in groups I-IV, classified in class 548. Typical examples of compounds, e.g. Example 402

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having pyrrolidine ring. Spiro-compounds of examples 274,355,393, and Example 377. If this group is elected further restriction election will be required as there are many unknowns.

VI. Claims(in part) 1,2,12,14,15,17-23,26,31-36,52,60, drawn to compounds, compositions,a method of use, and the first recited process of making Formula I wherein the cinnamide group is in ortho-position i.e. R1 = cinnamide. If this group is elected, further restriction/election will be required as there are many unknowns.

VII. Claims(in part)24,25, drawn to compounds, compositions,a method of use, and the first recited process of making Formula II compounds.If this group is elected, further restriction/election will be required as there are many unknowns.

Applicants have elected with traverse the species as represented by Compound 423 B specification page 383 which has a generic core: “ 6-membered heterocycle(piperidine)-phenyl-S-phenyl-CH=CH- CO-6-membered heterocycle(1,4-0xazine)”. This compound falls in above Group II. Claims(in part) 1,3-23,26-60, drawn to compounds, compositions, a method of use, and the first recited process of making Formula I phenyl ring is 4-substituted cinnamide,classified in class 544, subclasses 106,253,283; class 514 subclasses 295, 395.415,712.

The traversal is on the ground(s) that the subject matter of claims in groups I-VII are related through a common feature and that carrying out the search on the subject matter would not impose a serious burden on the examiner . This is not found persuasive because applicants'

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claims are drawn to (I) various compounds, (II) methods of using the said compounds, (III) methods of making the compounds. The grouping of claims according to the U. S. Patent classification system are clearly separate and distinct inventions. Thus, a search of all the groupings, would constitute an undue burden of search.

The requirement is still deemed proper based on sound scientific basis and is therefore made FINAL.

**II. Rejections withdrawn:** Applicants' arguments and remarks are considered favorably, and found persuasive. Therefore, rejections made under 35 USC 103(a) are now withdrawn.

**III. Rejections maintained:**

**IIIA.**

***Double Patenting***

Double Patenting rejections for claims 1,3-23,26-60 made in earlier Office Action Paper # 8 dated 2/27/02 against prior independent U.S. Application No. 09222491, filed 12/29/1998, now USP 6110922 and copending US Application No. 09695040 filed 10/24/2000, are maintained further for the reasons already stated in that action.

For applicants' ready reference, a copy of the STN/CAPLUS data for USP 6110922 i.e. CAS Abst. No/133:89514-2000:457022 is enclosed with this action as it shows the structures of the compounds claimed similar to compounds claimed herein. See e.g. compounds cited on pages 205-206 with Formula I wherein phenyl ring is 4-substituted cinnamide, i.e. R3 = cinnamide; wherein one of Ar and R3 (values consist) is a 6-membered heterocycle with 1 N, and additionally 1-3 heteroatoms.

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A timely filed terminal disclaimer in compliance with 37 CFR 1.321© may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

**IIIB.**

***Claim Rejections - 35 USC § 112***

Applicants' arguments and remarks are considered but not found persuasive for withdrawal for rejections. Rejections for claims 1,3-23,26-60 made under 35 USC 112 paragraph one are maintained further for the reasons already stated in the above mentioned earlier office action. paper #8 dated 2/27/02.

Following data from the journals provide state of art:

Mode of administration for preclinical trials for human:

- ◆ Zhou et al(PubMed Abstr.:11776041; also cited as Chin Med J. 1133/7,654-6(2000)) state that:" The efficacy of anti-inflammation and promotion of immuno-regulation especially on carrageenan and adjuvant-induced polyarthritis were shoiwn in animals. Coclusion: Human erythrocyte SOD injection is appropriate for prophylactic and therapeutic uses in clinical trials".

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- ◆ Mode of action for compounds having other structure(s) than the instantly claimed:  
Pillinger et al(PubMed Abstr.:9826736; also cited as Proc. Natl Acad Sci USA, 24/95-24, 14540-5 (1998)) state that:"These data are consistant with a role for Erk in stimulated neutrophil adhesion, and suggest that anti-inflammatory effects of salicylates may be mediated via inhibition of Erk signaliong required for integrin-mediated responses".
- ◆ Substituted diphenyl sulfides as selective serotonin transporter ligands:  
Emond et al (PubMed: 11881994; also cited as J. Med. Chem. 45/6,1253-8(2002)) state that:" Diphenyl sulfide derivatives substituted at the 1-, 2'-, and 4'- positions differently influence the SERT binding. (I). The nature of the substituent linked at the 1-position critically influences the SERT affinity.(II) Functions containing heteroatom at the 2'- position afford compounds with high SERT affinity.(III) The nature of the substituent at the 4'-position slightly influences the SERT affinity whereas stearic effect markedly decreases the SERT affinity".
- ◆ Screening of organosulfur compounds as inhibitors of human CYP2A6:  
Fujita et al(PubMed Abstr.:11408364; also cited as Dreug Metab Dispos, 29/7,983-9(2001)) state that:" 4,4'dipyridyl disulfide (and not diphenyl sulfide or dipyridyl sulfide) was found to be a potent and relatively selective inhibitor of CYP2A6".
- ◆ Cutting edge: a small molecule antagonist of LFA-1-mediated cell adhesion:  
Kelly et al(PubMed Abstr. 10553036: also cited as J Immunol, 163/10,5173-7(1999)).  
State that:" BRIT 377- (compound other than dipheny sulfide derivative) inhibits

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lymphocyte activity both in vitro and in vivo, in functional assays that require LFA-1-mediated cell adhesion. These results demonstrate that LFA-1-mediated leukocyte adhesion can be antagonized with noncharged, low m.w. molecules and suggests that the potential therapeutic value of adhesion inhibitors can be attained with a small, orally bioavailable compound".

Therefore, the quantity of experimentation need would be an undue burden to one skilled in the pharmaceutical arts since there is inadequate guidance given to the skilled artisan for the many reasons stated above.

#### **IV.**

#### ***Conclusion***

##### ***Allowable Subject Matter***

Claims related to compounds of invention of Group II as cited above would be allowable if rewritten to overcome the rejection(s) under 35 U.S.C. 112, paragraph one, and DP rejections set forth in this Office action and to include all of the limitations of the base claim and any intervening claims.

Method of use claims would be considered for allowance provided applicants resolve the various issues raised in the earlier Office Action as well as in this action, and provided applicants submit additional data as a support for the claim(s) as recited herein.

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**THIS ACTION IS MADE FINAL.** - Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sudhaker Patel, D.Sc. Tech. whose telephone number is (703) 308 4709.

The examiner can normally be reached on Monday thru' Friday from 8:30 AM to 5:00 PM. If attempts to reach the examiner by the phone are unsuccessful, the examiner's supervisor, Dr. Mukund Shah can be reached at (703) 308 4716.

A facsimile center has been established for Group 1600. The hours of operation are Monday through Friday, 8:45 AM to 4:45 PM. The telecopier numbers for accessing the facsimile machine are (703) 308-4556 or (703) 305-3592.

Any inquiry of general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308 1235.

*S. Blach*  
Sp/September 21, 2002.

*Mukund J. Shah*  
MUKUND J. SHAH  
SUPERVISORY PATENT EXAMINER  
GROUP 1600